Appendix

Syntheses methods

Unit-of analysis issues were handled as follows: In studies reporting on more than two treatment groups, three approaches were taken to avoid unit-of-analysis conflicts: In case of groups being comparable, we combined them. If additional groups used treatments not in accordance with current standard (e.g. multiple-step treatment without any root-canal medication), this group was omitted. If a factorial design was used (e.g. both groups were compared in vital and non-vital teeth), with separate reporting for all groups, we compared subgroups and handled them as if they were separate studies for meta-analysis.

Meta-regression was additionally performed. As some studies did not clearly state randomization (see above), a sensitivity analysis excluding these studies was performed. Similarly, as some studies reported results to have not been significantly different (but did not report on exact effect estimates), we imputed the number of events per group as the mean event rate in a sensitivity analysis, making best use of all available information. For subgroup comparisons, Chi-square test was performed. For meta-regression, the unrestricted maximum-likelihood method was used; Bonferroni adjustment to correct for multiple testing was planned, but not required, as no significant associations were found even without such correction.

Trial sequential analysis was performed. RIS was calculated based on type I error risk of $\alpha=0.05$ and a type II error risk of $\beta=0.20$ (equivalent to a power of 0.80). The control event proportion (i.e. event incidence in multiple-visit group) and the relative risk reduction (RRR) were used to estimate RIS. RRR was based on an a priori defined worthwhile interventional effect of 20% (lower effects might be worthwhile, but would increase RIS even further) (1, 2). RIS was diversity (heterogeneity) adjusted (DARIS). To assess if differences yielded by conventional meta-analysis are robust, TSA additionally estimates trial sequential monitoring boundaries (TSMB), i.e. statistical thresholds for significance which are adapted depending on the so far reached sample size. The Lan-DeMets version (3) of the O'Brien–Fleming

function (4) was used for calculating the TSMBs. In case the cumulative Z-value crossed the conventional boundary of significance (Z=±1.96) but not the TSMBs for benefit or harm, we defined such findings as spuriously significant. Firm evidence was assumed to be reached when the Z-curve crossed the TSMB for benefit or harm before the DARIS was reached. Effect estimates supported by only few small trials are thus handled stricter than those supported by large samples. In addition to such superiority/inferiority TSMBs, monitoring boundaries for futility were calculated (these indicate if further trial conduct is likely to be futile, i.e. if sufficient evidence has been accrued to claim non-inferiority of treatments). Further details regarding the applied method to calculate TSMB have been reported elsewhere (1). TSA was performed with TSA 0.9 (Copenhagen Trial Unit, Copenhagen, Denmark) (5).

Table S1: Excluded Studies

Soltanoff 1978 (6)	Selection bias (allocation according to tooth status)
O'Keefe 1976 (7)	Selection bias (allocation according to available time)
ElMubarak 2010 (8)	No RCT
Raju 2014 (9)	Did not compare 1- vs 2 visits
Xavier 2013 (10)	No clinical outcome
Bhagwat 2013 (11)	Did not compare 1- vs 2 visits
Roane 1983 (12)	No RCT
Oliet 1983 (13)	Selection bias (allocation according to patient acceptance, available time, symptoms of tooth)
Ether 1978 (14)	Not available
Eleazer 1998 (15)	no RCT
Fava 1989 (16)	Compared different techniques
Fox 1970 (17)	Did not compare 1- vs 2 visits
Genet 1986 (18)	Did not compare 1- vs 2 visits
Morse 1987 (19)	Did not compare 1- vs 2 visits
Yesilsoy 1988 (20)	Did not compare 1- vs 2 visits
Trope 1991 (21)	Did not compare 1- vs 2 visits
Koba 1999 (22)	Did not compare 1- vs 2 visits
Glennon 2004 (23)	Did not compare 1- vs 2 visits
Ng 2004 (24)	no RCT
Georgopoulou 1986 (25)	no RCT
Jurcak 1993 (26)	no RCT
Imura 1995 (27)	no RCT
Walton 1992 (28)	no RCT
Alacam 1985 (29)	Did not compare 1- vs 2 visits
Torabinejad 1994 (30)	Did not compare 1- vs 2 visits
Sjögren 1990 (31)	Did not compare 1- vs 2 visits
Siqueira 2002 (32)	Did not compare 1- vs 2 visits
Orstavik 1996 (33)	Did not compare 1- vs 2 visits
Perkruhn 1986 (34)	Did not compare 1- vs 2 visits
Kvist 2004 (35)	no clinical outcomes reported (CFU)
Rudner 1981 (36)	no RCT
Kenrick 1999 (37)	no RCT
Sjögren 1997 (38)	Did not compare 1- vs 2 visits
Maddox 1977 (39)	Did not compare 1- vs 2 visits
Sjögren 1990 (31)	no RCT
Fleming 2010 (40)	no RCT
Singla 2008 (41)	pulpectomy
Kalhoro 2009 (42)	no RCT
Shaikh 2013 (43)	Not available

Table S2: Risk of bias of included studies. Bias assessment followed guidelines outline by The Cochrane Collaboration (44).

	Sequence generation	Allocation Concealment	Blinding of operator	Blinding of examiner	Incomplete data	Selective reporting	Overall risk of bias
Akbar 2013 (45)	Unclear	Unclear	High	Low	Low	Low	Unclear/High
Albashaireh & Alnegreshi 1998 (46)	Unclear	Unclear	High	Low	Low	Low	Unclear/High
Al-Negrish & Habahbeh 2006 (47)	Unclear	Unclear	High	High	Low	Low	Unclear/High
DiRenzo 2002 (48)	Low	Low	Low	Low	Low	Low	Low
Dorsani 2013 (49)	Unclear	Unclear	High	Low	Low	Low	Unclear/High
Fava 1989 (50)	Unclear	Unclear	High	Low	Low	Low	Unclear/High
Fava 1994 (51)	Unclear	Unclear	High	Low	Low	Low	Unclear/High
Gesi 2006 (52)	Low	Low	High	Low	Low	Low	Unclear/High
Ghoddusi 2006 (53)	Unclear	Unclear	High	Low	Low	Low	Unclear/High
Ince 2009 (54)	Unclear	Unclear	Unclear	Low	Low	Low	Unclear/High
Jabeen 2014 (55)	Low	Low	Low	Low	Low	Low	Low
Liu & Leng 2013 (56)	Unclear	Unclear	High	Low	Low	Low	Unclear/High
Molander 2007 (57)	High	Unclear	High	Low	Low	Low	Unclear/High
Mulhern 1982 (58)	Low	Low	High	Low	Low	Low	Unclear/High
Oginni 2004 (59)	Low	Low	Low	Low	Low	Low	Low
Paredes-Vieyra 2012 (60)	Unclear	High	High	Low	Low	Low	Unclear/High
Pekruhn 1981 (61)	Unclear	Unclear	Unclear	Low	Low	Low	Unclear/High
Penesis 2008 (62)	Low	Low	Low	Low	Low	Low	Low
Peters and Wesslink 2002 (63)	Low	Unclear	High	Low	Low	Low	Unclear/High
Prashanth 2011 (64)	Unclear	High	High	High	High	Low	Unclear/High
Rao 2014 (65)	Unclear	High	Low	Low	Low	Low	Unclear/High
Risso 2008 (66)	Low	Low	Low	Low	Low	Low	Low
Singh and Kargh 2012 (67)	Unclear	High	Low	Low	Low	Low	Unclear/High
Trope 1999 (68), Waltimo 2005 (69)	Low	Low	Low	Low	Low	Low	Low
Wang 2010 (70)	Low	Low	High	High	Low	Low	Unclear/High
Weiger 2000 (71)	Unclear	High	High	Low	Low	Low	Unclear/High
Wong 2015a (72)	High	High	Low	Low	Low	High	Unclear/High
Wong 2015b (73)	Low	Unclear	High	High	Low	Low	Unclear/High
Yoldas 2004 (74)	Unclear	Unclear	High	Low	Low	Low	Unclear/High

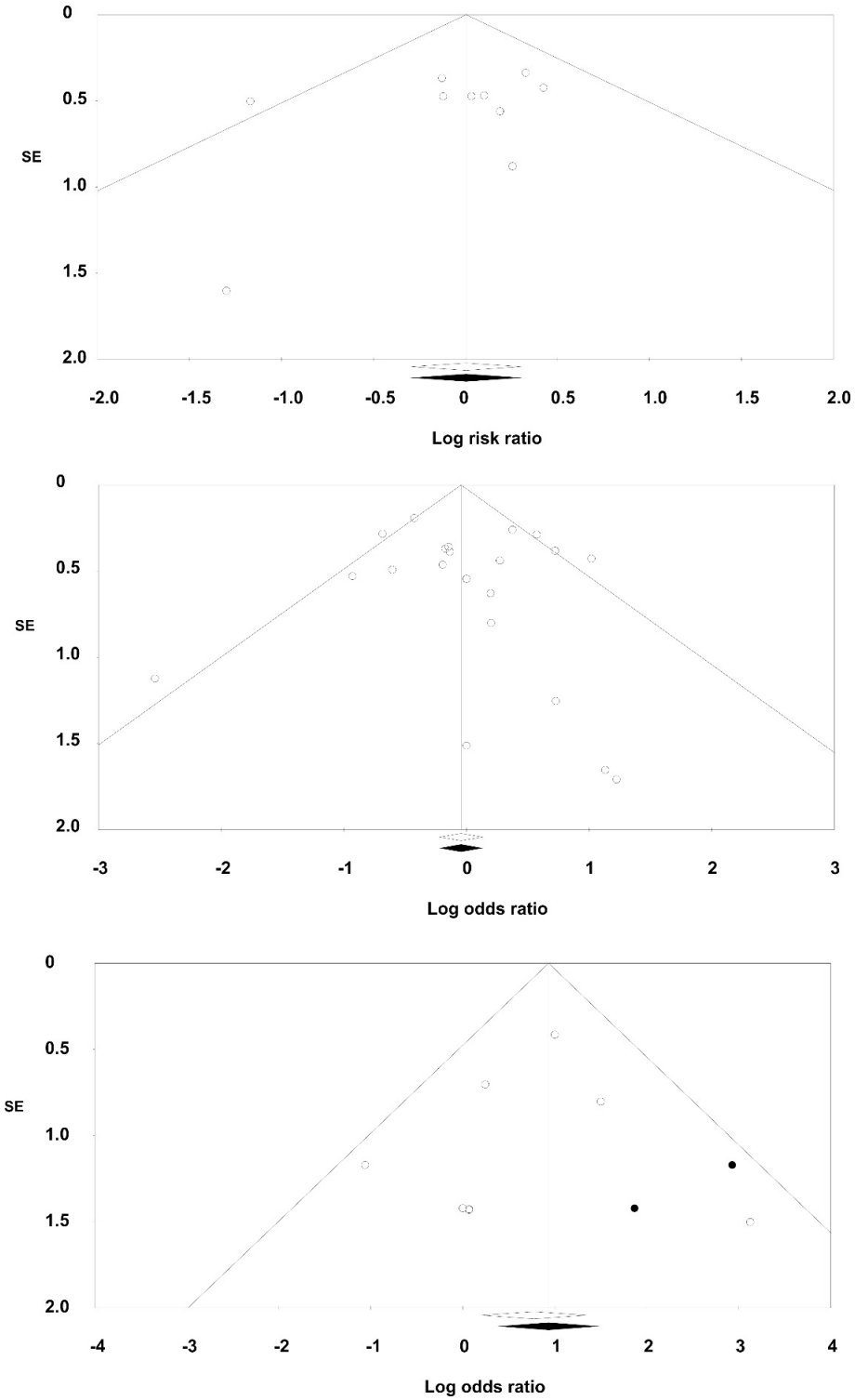

Figure S1: Funnel plots. (a) Risk long-term complications, (b) risk of experiencing any postoperative pain, (c) risk of experiencing a flare-up. Standard errors are plotted against logRR to estimate possible small study effects or publication bias via an asymmetry of the funnel. White circles: estimates reported by included studies, black balls: imputed estimates in case of suspected publication bias. White diamond: effect estimate based on included studies, black diamond: effect estimate based on included and imputed studies.

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